## REMARKS/ARGUMENTS

Prior to the entry of the foregoing amendments, claims 1-3, 8-17 and 32 were pending in this application and stood rejected on various grounds. Claims 1, 8,15, 16, and 32 have been amended, claim 17 has been canceled. The amendment of claim 1 is supported at least in paragraph [0078] of the specification. Specific support for the amendment of claim 8 is at least in paragraph [0067] of the specification. The other amendments are of formal nature. All amendments are fully supported by the specification as originally filed and do not add new matter. All amendments and cancellations were made without prejudice or disclaimer. Applicants expressly reserve the right to pursue any deleted subject matter in one or more continuing applications.

### Rejections Under 35 U.S.C. §112, First Paragraph – Enablement

Claims 1-3, 8-17 and 32 have been rejected as allegedly failing comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Claim 17 has been canceled. The rejection of the remaining claims is respectfully traversed.

In view of a similar rejection in the previous Office Action, in order to avoid unnecessary repetitions, Applicants' comments and arguments made in their response of March 7, 2006 are hereby expressly incorporated by reference.

According to the present rejection, *"the antibody 2C4 produced by hybridoma cell line deposited under ATCC Deposit No. HB-12697 recited in Claims 3, 9, and 31 are [sic] required to practice the claimed invention."* (Office Action, page 2, paragraph 7.) The Examiner notes that Applicants should provide assurances that the deposit was made under the terms of the Budapest Treaty and meets the criteria set forth in 37 C.F.R. §§1.801-1.809. Enclosed with the present Amendment and Response is a Deposit Statement by an Attorney of Record, which provides the requested assurances.

In addition, the Examiner appears to see the following issues regarding enablement:

(i) The claims encompassing the treatment (including prevention) of psoriasis in all mammals are allegedly not enabled.

The Examiner notes: *"the specification does not teach how to treat psoriasis in all mammal,"* or that *"any and all antibody that bind to human ErbB2 also bind to ErbB2 from other mammals."* The Examiner adds that the *"specification is silent as to whether the deposited*

*antibody 2C4 that binds to human ErbB2 also binds to ErbB2 from other mammal," "the specification does not teach any assay to identify which mammal within a given population who would or would not have psoriasis,"* and *"does not teach any vitro assay that is predictive of preventing psoriasis in all mammals."* (Office Action, page 2, paragraph 8; and paragraph bridging pages 3 and 4).

Without acquiescing to the rejection, or the Examiner's specific reasoning in support of this ground for rejection, the claims are now directed to the therapeutic treatment of humans, therefore, this issue associated with the treatment of non-human mammals is believed to be moot.

(ii) The prevention of psoriasis is allegedly not enabled (see, e.g. . Office Action, page 3, second paragraph and paragraph bridging pages 3 and 4). Without acquiescing to this ground for rejection, the claims, as currently amended, are drawn to methods for the "therapeutic treatment" of psoriasis, therefore, this issue is believed to be moot.

(iii) With regard to claim 8, the Examiner takes the position that there is insufficient guidance as to which "biological characteristic" of monoclonal antibody 2C4 an antibody should have for preventing psoriasis. (Office Action, page 4, second full paragraph.) First of all, the claims, including claim 8, are now directed to the "therapeutic treatment" of psoriasis. Secondly, claim 8 has been amended to recite an antibody that "binds the same epitope in the extracellular domain of ErbB2 as that bound by monoclonal antibody 2C4." Accordingly, this issue is believed to be moot.

(iv) With regard to claim 9, the Examiner notes that there is *"insufficient guidance as to the binding specificity of any antibody that comprises antibody 2C4 or humanized 2C4."* (Office Action, page 4, second full paragraph.) Applicants respectfully disagree. An antibody that comprises antibody 2C4 or humanized antibody 2C4 will, by definition, retain the binding specificity of 2C4. Thus, for example, a 2C4 antibody conjugated with a cytotoxic agent, which is specifically encompassed by claim 13, would be an antibody "comprising" antibody 2C4 (and thus retaining its binding specificity) but also including a cytotoxic agent. Such antibodies are taught, for example in paragraph [0140] and paragraphs [0195] – [0205] of the specification. Another example of antibodies that "comprise" antibody 2C4 or humanized antibody 2C4 are conjugates in which 2C4 is conjugated to a prodrug-activating enzyme which converts a prodrug to an active drug, This approach (referred to as "ADEPT") was well known in the art at the

priority date of the present application, and is described in detail in paragraphs [0206] – [0210] of the specification. Accordingly, one of ordinary skill in the art at the priority date of the present application would have been able to make and use such antibodies for the therapeutic treatment of psoriasis without undue experimentation.

(v) With regard to claims 15 and 32, the Examiner takes the position that *"there is inadequate guidance as to any and all ErbB antagonists, any immunosuppressive agent, any chemotherapeutic agent, any cytotoxic agent, any growth inhibitory agent, and anti-hormonal compound, any cardioprotectant[,] any cytokine, and any TNF antagonist without the chemical structure, much less which combination with antibody that binds to ErbB2 is effective for treating psoriasis and which combination is effective for preventing psoriasis."* With regard to cardioprotectants, the Examiner specifically notes that *"there is no disclosure of any cardioprotectant in combination of anti-ErbB2 that could prevent myocardial dysfunction (i.e., cariomyopathy [sic] and/or congestive heart failure associated with anti-ErbB2 treatment for psoriasis."* (Office Action, page 4, third and fourth full paragraphs.)

Applicants respectfully disagree, and traverse this ground for the lack of enablement finding.

Because the adequacy of the disclosure is judged from the perspective of one of ordinary skill in the art, a *"patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987).

The present invention is based on the use of anti-ErbB2 antibodies, which are effective in and by themselves in the therapeutic treatment of psoriasis. Some claims, such as claims 15 and 32 provide that such antibodies can, optionally, be administered with other therapeutic agents, such as those listed in claims 15 and 32. Immunosuppressive agents, chemotherapeutic agents, cytotoxic agents, growth inhibitory agents, anti-hormonal compounds, cardioprotectants, cytokines, and TNF antagonist were well known in the art at the priority date of the present application, and thus under the standard established by the CAFC and articulated in *Spectra-Physics*, a specific teaching is not only not needed by should preferably omitted. Nonetheless, the present application does provide such teaching, for example in paragraphs [0104] – [0110] and [0112]. Specific, commercially available, TNF antagonists (Ethanercept (ENBREL®.; Amgen), Infliximab (REMICADE®.; Centecor), D2E7, or CDP-870 (Celltech)) are also specifically mentioned, e.g. in paragraph [0288]. Similarly, specific, commercially available IL-

1 and IL-10 antagonists are taught in the same paragraph. It is inconceivable how, in view of the wealth of knowledge about these types of agents available in the art at the time the present invention was made, and the extensive teaching provided in the specification, the Examiner can take the position that such agents are not enabled, or that enablement for such agents would require the disclosure of their chemical structures. Since the Examiner is clearly applying an improper legal standard, contrary to well established case law, this reason for a finding of lack of enablement is believed to be unfounded, and should be withdrawn.

(vi) The Examiner asserts that the claims are not enabled, since (1) there are unlimited numbers of antibodies that bind ErbB2; (2) "there is not a single working example" that such antibody could treat psoriasis in human; (3) Sauder et al., of record, teach that psoriasis cannot be cured; (4) Giaccone et al., of record, teach that "predicting the future for patients using EGF receptor targeted agent [sic] is unpredictable"; (5) Ngo et al., of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change and which are critical to maintain the protein's structure/function will require guidance; (6) Mason et al., of record, reach that in activin A even a single amino acid substitution "fails to maintain either the structure and/or functions." In addressing Applicants' response to a prior similar rejection, the Examiner notes that the use of MCF7 breast cancer cell in Example 4 is not an appropriate model for a method of treating psoriasis "*because psoriasis is a chronic T cell mediated inflammatory skin disease and no cure for psoriasis has ever been found,*" and the "*art does not teach the use of breast cancer cell as a model for psoriasis.*" (Office Action, page 6, last paragraph.)

Before turning to the specifics of this reasons for rejection, it is again emphasized that the claims are directed to the "therapeutic treatment" of psoriasis, and thus neither a "cure" nor a method of "prevention" is claimed. Accordingly, the statement that psoriasis cannot be cured (Sauder et al., reason (3) above) is irrelevant for assessing enablement. Similarly, the Examiner's similar statement with regard to Example 4 is believed to be irrelevant, since a "cure" of psoriasis is not claimed. Indeed, while psoriasis is a chronic disease with no known cure, at the effective filing date of this application, there were commercially available drugs on the market for the treatment of psoriasis. Thus, as stated in Example 5, psoriasis patients have successfully responded to treatment with various immunomodulatory or immunosuppressive agents, *e.g.*, cyclosporine, tacrolimus (FK506), and DAB389 IL2, which selectively target activated T-cells. Furthermore, in October 2003, the FDA approved the anti-CD11a monoclonal

antibody, RAPTIVA® (efalizumab; Genentech, Inc.) for the treatment of moderate-to-severe plaque psoriasis in adults 18 years or older. Thus, one of ordinary skill in the art at the effective filing date of this application would have fully accepted the monoclonal antibody treatment of psoriasis as credible.

Turning to the other points made by the Examiner, the MCF7 breast cancer cell line is not intended to be a model of psoriasis but is highly relevant to identifying agents useful in the treatment of psoriasis. The data presented in Example 4, which are based on the use of this cell line, establish that monoclonal antibody 2C4 inhibits ligand initiated ErbB signaling through two major signal transduction pathways: the MAP kinase and P13 kinase pathways. It was known at the priority date of this application, and is confirmed, for example, by Haase et al., J. Clin. Invest 108:527-536 (2001) (copy enclosed) that MAP kinase activation is responsible for epidermal hyperproliferation in psoriasis. Thus, blocking signaling through the MAP kinase pathway by the antibodies herein creates a reasonable expectation that epidermal hyperproliferation associated with psoriasis will be inhibited. This is also believed to address the Examiner's comment that the "specification does not disclose how blocking 2C4 from binding to ErbB2 is effective for treating/preventing psoriasis." (Page 4 of the Office Action.) The specification is addressed to those of ordinary skill in the art at the time the claimed invention was made. Since such persons of ordinary skill were aware of the pivotal role of MAP kinase activation in hyperproliferation in psoriasis, based on the data and explanation provided in the specification an ordinary artisan would clearly understand how 2C4 and other antibodies competing with 2C4 for ErbB2 binding would be expected to be effective in treating psoriasis.

In view of the present explanation and arguments, the Examiner is respectfully requested to reconsider and withdraw the rejection of the claims as currently pending.

**Rejections Under 35 U.S.C. §112, First Paragraph – Written Description**

Claims 1-3, 8-17 and 32 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claim 17 has been canceled. The rejection of the remaining claims is respectfully traversed. In order to avoid unnecessary repetitions, Applicants' arguments in response to an earlier similar rejection are hereby expressly incorporated by reference.

In the present rejection, after acknowledging the specific teaching in the specification of ErbB2 antibodies 7C2, 7F3, 4D5, and 2C4, and the ability of 2C4 to inhibit MAPK kinase activation, the Examiner advances the following reasons in support of the rejection:

(i) There is no adequate written description for the efficacy of such antibodies in all mammals. Since the claims are directed to the therapeutic treatment of humans, this reason is believed to be moot.

(ii) With regard to claim 8, the Examiner notes that there is inadequate written description about which "biological characteristic" of monoclonal antibody 2C4 "that any and all antibody should have for treating psoriasis." The current amendment of claim 8, which now recites antibodies that bind the same epitope in the extracellular domain of ErbB2 as that bound by 2C4, is believed to obviate this rejection. It is noted, however, that claim 8 has been amended without acquiescing to the rejection, or the Examiner's point of view underlying the rejection, and serves merely to expedite the prosecution of this application.

(iii) With regard to claims 15 and 32, the Examiner notes that there is "inadequate written description about of any and all ErbB antagonists, any immunosuppressive agent, any chemotherapeutic agent, any cytotoxic agent, any growth inhibitory agent, and anti-hormonal compound, any cardioprotectant, any cytokine, and any TNF antagonist without the chemical structure, much less in combination with antibody that binds to ErbB2 for treating psoriasis.

This reason for the present rejection is vigorously traversed.

The Examiner's attention is specifically directed to the Federal Circuit's recent decision in Capon v. Eshhar v. Dudas (418 F.3d 1349: 2005 (U.S. App); 76 USPQ (BNA) 1078) where the Federal Circuit held that the disclosure of a complete nucleotide sequence is not required to meet to written description requirement when a chimeric gene is claimed. In Capon, the USPTO's Board of Patent Appeals and Interferences (the Board) rejected a claim to a chimeric DNA invention under the test of Eli Lilly, finding that "the parties' claim is not described in their specifications . . . by reference to . . . the structure, formula, chemical name, or physical properties of many protein domains." Capon, 418 F.3d at 1355.

In explaining its ruling overturning the Board's decision, the Federal Circuit reaffirmed that "The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented." The Court added, however, that:

*The descriptive text needed to meet [the written description requirement] varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. . . [T]he law . . . will vary with differences in the state of the knowledge in the field and differences in the predictability of the science.*

Ibid, at 1357.

The Federal Circuit went on the clarify:

*The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described the same way .* Ibid, at 1358.

Applying this standard to the present invention, Applicants submit that the invention claimed in the present application is in full compliance with the written description requirement.

The present invention is based on the use of anti-ErbB2 antibodies, which are effective in and by themselves in the therapeutic treatment of psoriasis. Some claims, such as claims 15 and 32 provide that such antibodies can, optionally, be administered with other therapeutic agents, such as those listed in claims 15 and 32. Immunosuppressive agents, chemotherapeutic agents, cytotoxic agents, growth inhibitory agents, anti-hormonal compounds, cardioprotectants, cytokines, and TNF antagonist were well known in the art at the priority date of the present application, along with their respectively structures. Specific, commercially available, TNF antagonists (Ethanercept (ENBREL®.; Amgen), Infliximab (REMICADE®.; Centecor), D2E7, or CDP-870 (Celltech)) are also specifically mentioned, e.g. in paragraph [0288]. Similarly, specific, commercially available IL-1 and IL-10 antagonists are taught in the same paragraph. Thus, under the standard reiterated and articulated by the CAFC *Capon*, a specific disclosure of the structures of such additional agents is not required. These additional agents are adequately described by reference to known information that was available in the art at the effective filing date of this application. Accordingly, this reason for the present rejection is clearly unsupported by and contrary to applicable case law and should be withdrawn.

(iv) The Examiner notes that the four specific deposited antibodies that bind to human ErbB2 are not representative of all antibodies that "bind to any and all ErbB2, and second therapeutic agent or second drug for treating or preventing psoriasis in all mammals." The claims are directed to the treatment of humans, and therefore this reason for the present rejection is believed to be moot.

**New Rejection Under 35 U.S.C. §103(a)**

Claims 1-2, 8-17, and 32 have been rejected as allegedly being unpatentable over WO 01/15730, in view of WO 9802540 and Feldman et al., Dermatol Online J. 6(1):4, September 2000.

WO 01/15730 was cited for its teaching a method of treating benign hyperproliferative epithelial, inflammatory angiogenic immunological disorders by administering an effective amount of an antibody that binds ErbB2, including a humanized version of 4D5, 7C2, 7F3, 4D5, 2C4. The Examiner notes that the "claimed invention differs from the teachings of the reference only in that the method wherein the disease is psoriasis [sic]."

WO 98/02540 is cited for its alleged teaching that ErbB2 plays a role in psoriasis and a method of treating psoriasis by administering to the mammal an agent that blocks the ErbB2 ligand from binding to its receptor ErbB2, such as a soluble ErbB2 receptor. The Examiner adds that this PCT publication also teaches that "blocking ErbB2 using ErbB antagonist such as ErbB2 and ErbB3 or ErbB2 and ErbB4 fused to Fc prevents using ErbB ligand from binding and activation of the ErbB receptor."

Finally, the Examiner cites Feldman et al. as allegedly teaching a method of treating psoriasis by various immunosuppressive agents or a combination of such agents, and for teaching "a combination of modalities [that] can be used to enhance the therapeutic effect and minimize the adverse effects that could result from excessive use of one agent."

From this, the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat psoriasis by substituting the ErbB2-IgG that blocks ErbB2 ligand from binding to ErbB2 as taught by the WO 98/02540 publication for the antibody or Fab that binds to ErbB2 and thereby preventing the binding of ErbB2 ligand to its receptor as taught by the WO 01/15730 publication in combination with a second therapeutic agent." The Examiner adds that from the "combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention."

Applicants disagree and respectfully traverse the rejection.

Applicants maintain that the Examiner failed to provide a sufficient showing why a skilled person, confronted with the same problem as the present inventors and with no knowledge of the claimed invention, would have been motivated as of the effective filing date to select the

elements from the cited prior art references for combination in the manner claimed in the present application. In addition, Applicants reiterate their position, expressed in earlier responses, that psoriasis has acquired a separate place in the art, and thus, the fact that certain inflammatory or immunologic disorders are described to respond to a treatment, does not create a reasonable expectation that psoriasis could be treated in a similar manner. In view of this distinction, one of ordinary skill in the art at the time the present invention was made would not have had any motivation to combine WO 01/15730 and WO 98/02540. Indeed, the only motivation to make the purported combination derives from the disclosure of the present application, and is the result of an impermissible hindsight reconstruction of the claimed invention.

Applicants further submit that even if WO 01/15730 and WO 98/02540 could be properly combined, they would still not make obvious the claimed invention. WO 01/157030 was cited for its teaching of the treatment of various non-malignant conditions, in particular inflammatory and immunologic conditions, using ErbB2 antibodies. WO 98/02540 teaches to use of heteromultimeric immunoadhesins, including the extracellular domains of two at least two different ErbB receptors (*e.g.,* ErbB2/ErbB3, ErbB2/ErbB4, ErbB3/ErbB4), to treat psoriasis. At the priority date of the present invention, based on these two disclosures, without the knowledge of the present invention, one of ordinary skill would not have concluded that antibodies, which bind ErbB2 could treat psoriasis with a reasonable expectation of success.

Finally, it is emphasized that psoriasis is a chronic disease that is difficult to treat. A reasonable expectation that such treatment is likely to work by following the methods of the present invention has only been created by demonstrating the ability of the antibodies herein to block signaling through the MAP kinase pathway, the activation of which was, in turn, known to be responsible for epidermal hyperproliferation in psoriasis (see, e.g. Haase et al., *supra*).

Since the cited combination of references did not create a reasonable expectation that psoriasis could be successfully treated with the antibodies herein, without undue experimentation, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Applicants note and acknowledge that claim 3 has been acknowledged to be free of prior art, but submit that all claims are free of prior art and in *prima facie* condition for allowance. Accordingly, an early issuance of a Notice of Allowance is respectfully solicited.

Please charge any additional fees, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39766-0205**).

Respectfully submitted,

Date: March 28, 2006

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3/27/07 4:38 PM (39766.0205)